Estimating the True Respiratory Mechanics during Asynchronous Pressure Controlled Ventilation

D.O. Kannangara[1], F. Newberry[1], S. Howe[1], V. Major[1], D. Redmond[1], A. Szlavecs[2], Y.S. Chiew[3], C. Pretty[1], B. Benyo[2], G.M. Shaw[4], J.G. Chase[1]

[1]Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand
[2]Department of Control Engineering and Information, Budapest University of Technology and Economics, Budapest, Hungary
[3]School of Engineering, Monash University, Bandar Sunway, Malaysia
[4]Department of Intensive Care, Christchurch Hospital, Christchurch, New Zealand

Abstract

Mechanical ventilation (MV) therapy partially or fully replaces the work of breathing in patients with respiratory failure. Respiratory mechanics during pressure controlled (PC) or pressure support (PS) are often not estimated due to variability induced by patient's spontaneous breathing effort (SB) or asynchronous events (AEs). Thus for non-invasive model-based MV with PC/PS, there is a need for improved estimation of respiratory mechanics. An algorithm is proposed that allows for the improvement of respiratory system mechanics estimation during pressure controlled ventilation, while providing a means of quantifying AE magnitude as one indicator of patient-ventilator interaction, which may be valuable to clinicians to monitor patient response to care. For testing, 10 retrospective airway pressure and flow data samples were obtained from 6 MV patients, with each data sample containing 450-500 breaths. All data samples with AE present experienced a decrease in 5th to 95th range (Range90) and mean absolute deviation (MAD) for the estimated respiratory system elastance after reconstruction. These results suggested improved in respiratory mechanics estimation during pressure controlled ventilation. The median [maximum (max), minimum (min)] decrease in MAD was 29.4% (51%, 18.6%), and the median (max, min) decrease in Range90 divided by median respiratory system elastance was 30.7% (48.8%, 6.4%). The algorithm is robust to many different spontaneous breathing efforts, asynchrony shapes and types. The proposed algorithm demonstrates the potential to effectively improve respiratory mechanics and quantify the magnitude of AEs.

1.0 Introduction

Patients with respiratory failure require mechanical ventilation (MV) for breathing support [1-3]. To aid the patient's recovery from the underlying disease, his/her work of breathing is partially or fully replaced by the mechanical ventilator [3]. Common MV modes can be divided into volume controlled (VC) or pressure controlled (PC). While VC is able to provide a fixed tidal volume delivery, some clinicians prefer PC mode. This mode can limit the maximum driving pressure delivery during MV. Limiting the maximum pressure can prevent patients from incurring pressure induced lung injury, also known as barotrauma [4, 5]. PC ventilation is often extended to pressure support (PS) ventilation, allowing the patient to breathe spontaneously to potentially aid recovery [6].

During PC/PS ventilation, a predefined driving pressure and a corresponding tidal volume are delivered to the patient. Thus, the delivered tidal volume can be variable, depending on the patient's condition. This variability may be beneficial to patients but it affects model-based breath-to-breath respiratory mechanics estimation, causing inconsistency. This inconsistency in respiratory mechanics estimation is further aggravated during PS mode where patients exhibit spontaneous breathing efforts (SB) or an asynchrony event (AE) occurs. An example of the flow and pressure waveforms exhibited in normal and asynchronous breaths is shown in Figure 1. In pressure control MV, the pressure waveform is the controlled variable and therefore is relatively unaffected.

Asynchrony events are problematic as they obscure the process of identifying the underlying patient-specific respiratory mechanics [7], and have also been linked to poor clinical outcomes including increased mortality [8-10]. A specific problem of consistent asynchronous breaths occurring during PS ventilation, termed ‘reverse triggering’, was first documented by Akoumianaki et al. in 2013 [7]. It was noted that this form of neuromechanically coupling has been largely undocumented by clinicians and can prevent accurate determination of the underlying respiratory mechanics [7]. In fact, much of the breathing data utilized in this study exhibits the characteristics of reverse-triggering. To the knowledge of the authors, there are no current extensively tested methods for identifying patient respiratory mechanics during asynchronous pressure controlled MV without the use of invasive protocols or equipment [11, 12]. Because of this, during PC/PS ventilation mode, relatively little model-based respiratory mechanics estimation is performed and it is not used to guide mechanical ventilation. A successful method to allow real-time monitoring of respiratory mechanics in pressure-controlled MV patients must be able to separate the asynchronous breathing or patient’s own spontaneous breathing efforts from the support by the ventilator.

While the specific phenomenon of reverse-triggered breaths during phenomenon has only been brought to attention in the past few years, the problem of determining the patient’s underlying respiratory mechanics during spontaneous breathing has been a long-time subject of research. The flow interrupter technique (FIT), a method of determining the respiratory mechanics during spontaneous breathing, was first introduced by Von Neergaard and Wirz in 1927 [13] and has been refined in more recent years [14, 15]. However the method involves obstructing the flow of air delivered and is most suitable for non-intubated patients. It is not compatible with continuous monitoring of respiratory mechanics and does not allow for separation of spontaneous breathing efforts from those of the ventilator [16]. Similarly, body plethysmography allows for measurement of airway resistance and therefore can be utilized to calculate elastance [17]. It requires the patient to be situated in a glass container during use and therefore is not appropriate for use in intensive care.

Methods developed for monitoring of respiratory mechanics in intubated, mechanically ventilated patients have also been developed, such as the transient flow reduction technique described by Younes et al. [16]. However, similar to FIT, the technique requires the flow to be obstructed during measurements and is therefore not suitable for real-time continuous monitoring of respiratory mechanics. Dubois et al. developed a forced oscillation technique in which small-amplitude pressure oscillations are superimposed onto a regular breath, allowing for frequency domain analysis of respiratory mechanics [18, 19]. Such methods have been demonstrated to allow for titration of PEEP through determining a patient’s respiratory mechanics [20]. However, implementation into clinical practice would require modification to current ventilator hardware. Other methods include the measurement of esophageal pressure to account for pressure changes in the pleural cavity due to muscular efforts [21]. Such methods are invasive due to balloon catheterisation of the esophagus and thus have not seen widespread clinical application [22].

Non-invasive model-based methods for determining respiratory mechanics during asynchronous MV have only appeared in recent years. These methods only require acquisition of patients airway pressure and flow data from the ventilator. Redmond et al. developed a method for reconstructing a pressure waveform, however this only applies to volume controlled MV [23]. A different approach is taken by Rigo et al. in which breathing cycles are uniquely selected to estimate respiratory mechanics [24]. While such an approach may be effective for times in which only some breaths are affected by spontaneous breathing efforts, it may not be suitable for periods of continuous entrainment in which every breath is asynchronous, as has been seen in the data utilized in this study. For PC mode, Vicario et al have recently developed a constrained optimisation method to account for patient diaphragmatic effort [25]. The method demonstrates an ability to improve estimation of respiratory mechanics in mechanically ventilate patients, however the method has yet to be extensively tested on human data.

Thus, there is still a need to improve current capabilities of identifying patient respiratory mechanics during pressure controlled MV, so that model-based methods of guiding treatment may take place. Additionally, there is a need to quantify the size or magnitude of AEs so that clinicians may be provided with valuable information on patient-ventilator interaction during the course of treatment.

This study presents a proof of concept iterative method to improve model-based respiratory mechanics estimation during pressure controlled ventilation. Specifically, an iterative interpolative flow reconstruction method is used. This method operates by identifying whether a pressure controlled or pressure supported breath is distorted by spontaneous breathing effort or an AE. This method then reconstructs the affected airway flow to a single compartment respiratory model airway flow profile. This method yields a pseudo airway flow profile that is unaffected by spontaneous breathing or asynchrony, allowing estimation of the unaffected, underlying patient-specific respiratory mechanics, while quantifying the magnitude of AEs.

2.0 Method

2.1 Patient Data

Airway pressure and flow data from MV patients admitted to the Christchurch Hospital intensive care unit (ICU) were used in this study. The patients were ventilated with Puritan

Bennett 840 ventilation using synchronous intermittent mandatory ventilation (SIMV) pressure controlled mode to achieve tidal volume of 6~8 ml/kg [26]. Ten data samples, each having 450-500 breathing cycles (~30 minutes) were extracted from 6 patients included in this study. It is assumed that underlying respiratory mechanics and patient condition do not change significantly over a short period of time. Therefore, the respiratory system elastance, E identified from reconstructed flow profiles is expected to be far more constant than far those affected by SB or AE. All data were sampled at 50 Hz and processed using MATLAB (R2014a, The Mathworks, Natick, Massachusetts, USA).

2.1.1 Ethics, Consent and Permissions

Acquisition and use of patient data was approved by the New Zealand Southern Region Health and Disability Ethics Committee (HDEC) under informed consent (13/STH/84 and URA/12/EXP/022).

2.2 Reconstruction Method

In this section, the sequence of the iterative interpolative flow reconstruction method is presented. Figure 2 illustrates an example of the airway flow reconstruction for an asynchronous breathing cycle in 9 total steps. Each step is specifically defined.

Step 1: Filtering data:

Pressure and flow waveforms are first filtered to remove noise, using a first order zero-phase Butterworth Filter with a normalized cut-off frequency of 0.3 Hz. An example of raw and filtered flow data is shown in Figure 2, Step 1.

Step 2: Locating the shoulders of airway pressure:

The left and right shoulders of the airway pressure curve are identified. The location of these shoulders is important because the fitting of physiological parameters is most dependent on this region. The identified shoulder locations are shown as crosses on the pressure curves in Figure 2, Step 2.

A first approximation to the location of the left shoulder is found by taking the maximum of the shear transform [27] between the first data point and the point of maximum pressure. The second shoulder, corresponding to the end of inspiration, is found by taking the maximum of the shear transform between the point of maximum pressure and the point of minimum flow. The shear transform lines for the first and second shoulders are indicated in Figure 2, Step 2 by the dashed and solid lines, respectively.

For a more reliable identification of the left shoulder, a second shear transform is performed. The left shoulder is defined as the location of the maximum of the shear transform between the first data point and a quarter of the way between the first approximation to the shoulder and the end inspiratory point. For most cases, the final identified location of the left shoulder and the first approximation will be the same.

Step 3: First single compartment model fitting:

A single compartment linear lung model is then fit to the data using an integral based linear regression method [28], with the model defined:

$$R\frac{dV(t)}{dt} = (P(t) - P_{PEEP}) - EV(t) \quad (1)$$

Where R is the respiratory system resistance, V is the tidal volume, t is time, P is the airway pressure, P_{PEEP} is the offset pressure or positive end-expiratory pressure (PEEP), E is the respiratory system elastance.

During PC ventilation, pressure is the controlled variable in this case, the model is fit to the volume and flow data and is indicated by the dashed line in Figure 2, Step 3. The model is fit between the two identified shoulders to avoid non-physiological changes in R and E induced by the mechanics of the ventilator. The PEEP is defined as the minimum pressure between the first data point and the end inspiratory point. If the area between the model fit and actual flow curves is below a user specified threshold, the flow is deemed to be free of patient induced effort or with no AE, the flow reconstruction will not occur.

Step 4: Locating patient-induced effort:

The intersections between the flow data and the model fitted curve are identified. Intersections due to asynchrony are selected based on the gradient of the pressure curve at the crossings. Asynchronous regions can be identified by a rise in an otherwise monotonically decreasing flow inspiration waveform. If the asynchrony is significant in magnitude, it will cause an intersection between the model fit and raw flow data at this upwards sloping region. Therefore if the gradient at an intersection is positive, the breath is detected as asynchronous. The asynchronous crossing is shown in Figure 2, Step 4 as a cross.

Step 5: Reduction of patient-induced effort:

Inspiratory flow unaffected by patient efforts takes a ramp shape. Therefore, the asynchronous crossings are used to estimate the appropriate gradient of the ramp. The flow profile is constructed by using a straight line intersecting two points, referred to from here as 'flow reconstruction points'.

The first flow reconstruction point used is two data points after the first fit point of the flow data. The first two data points are not used as there is usually some error in the data close to the maximum of the flow due to interaction between the patient and the ventilator.

The second flow reconstruction point used is the point halfway (in time) between the identified asynchronous crossing and the minimum of flow up to that point. This choice results in the estimated true ramp flow being constructed underneath the area of identified asynchrony and, as such, is a more accurate estimate of the unaffected flow waveform. The two flow reconstruction points are shown as crosses in Figure1, Step 5, and the reconstructed flow is shown as the thin line.

Step 6: Single compartment model refitting

The single compartment lung model is fit a second time to the new reconstructed flow in Figure 2, Step 6. The refit curve is shown as the dashed line. The magnitude of asynchrony is found by taking the absolute value of the area between the final curve fit and the flow data.

Step 7a: First special case - Breaths with early asynchrony, initial reconstruction:

Note that the choosing of the two points in Step 5 for flow reconstruction is only valid if the asynchrony is sufficiently far away from the beginning of inspiration. If the asynchrony is too close to the flow maximum, then there will be no region unaffected by asynchrony between the two points usually used. The estimation of the ramp gradient will thus fail.

Therefore, if the first asynchronous crossing detected is within 8 data points of the first fit flow point, a modified approach is taken to reconstruct the flow. In this case, the second flow reconstruction point is the point of last crossing in inspiration between the fit flow and the actual flow data. This region is the most likely to be free of asynchrony if there is an asynchrony near the beginning of the breath. In addition, having the maximum distance between the two flow reconstruction points, it results in the least error. After this point, the reconstructed flow is set as the same as the actual flow. An example of a flow reconstruction with an early asynchrony is shown in Figure 2, Step 7a, with the flow reconstruction points indicated by crosses and thin lines indicating the flow reconstruction.

Step 7b: First special case – Breaths with early asynchrony, iterative reconstruction

The reconstruction method for early asynchronies usually results in the flow curve being reconstructed too high, resulting in an incorrect E estimation. Therefore, an iterative procedure is taken, using the model fit to guide further reconstruction. A new flow curve is constructed using the refitted model curve. The first flow reconstruction point is the same as in Step 6. However, the second flow reconstruction point used is the new intersection at the end of the flow curve between the data and the new model fit. Using this method, the flow is iteratively driven down until convergence or a set number of iterations is reached. This method typically converges within 4 iterations. A convergence criterion could be applied based on the change in the final pressure intercept, however for this study the number of iterations was set to be constant at 5. An example of the iterative procedure is shown in Figure1, Step 7b, with the final reconstruction indicated by the lowest solid line.

Step 7c: Second special case – Breaths where a linear extrapolation is not suitable:

Another special case is where extrapolating a line would result in negative flow. This issue occurs in situations where either the actual flow becomes negative or where the model fit approaches zero flow early and levels out. In these cases, the flow data is kept the same up to the crossing before the first asynchronous crossing. After this point, the initial model fit is used instead of the raw data. This approach generally acts to raise the final model fit slightly, which does not include a negative flow in inspiration, as seen in the magenta line in Figure 2, Step 7c. Figure 3 shows a basic flowchart of the process described.

2.3 Data Analysis

2.3.1 Respiratory mechanics estimation

The pseudo airway flow generated by the IIFR presented is used for respiratory mechanics estimation. The estimated respiratory mechanics are compared to the respiratory mechanics estimated using the original airway flow prior to reconstruction. A two sample Kolmogorov-Smirnov test is used to test the difference of respiratory mechanics distribution. A p-value of < 0.05 is considered statistically significant.

The magnitude of asynchrony for each asynchronous breathing cycle can be estimated as the difference between the pseudo reconstructed airway flow during inspiration and the asynchronous pressure:

$$A = \frac{\int_{t_{IS}}^{t_{IE}} |Q_a - Q_r| dt}{\int_{t_{IS}}^{t_{IE}} Q_a dt} \tag{2}$$

Where Q_r is the reconstructed airway flow, and Q_a is the asynchronous flow. The limits t_{IS} and t_{IE} are the times of the occurrence of the 'shoulders' of the pressure curve at the start and end of inspiration respectively. Equation 2 can be used for both the initial model fit, and the reconstructed model fit. Although reconstruction can take place on all breaths where an asynchronous crossing has been detected, if the initial model fit error area is less than 5%, calculated using Equation 2 for the model fit and data, the original value of elastance is used for the elastance estimate. This avoids needless changes to the estimated elastance in breaths with a very low level of asynchrony. An exception to this is where the initial model fit is satisfactory but the breath is actually highly asynchronous, with a threshold on the final asynchronous area of 9% where all breaths are considered asynchronous regardless of the initial model fit. These thresholds were determined by inspecting breaths with low or high levels of asynchrony.

2.3.2 Respiratory system elastance variation and spread analysis

To analyse the spread and variation of the estimated respiratory system elastance, E, the mean absolute difference (MAD) and Range90 is calculated [29]. Range90 is the difference between the 95th percentile and the 5th percentile of the E distribution. To normalise the results, the Range90 value is divided by the median non-asynchronous E value. Hence, the spread or the range of the parameter can be quantified and compared within different data sets, as it is a form of dimensionless variation.

3.0 Results

The algorithm was run on all data sets. Four example reconstructions on different asynchrony shapes are included in Figure 4, with the dashed line indicating the reconstruction. Note that any ‘wobbles’ in the reconstructed flow fit are generally due to the pressure waveforms being slightly affected by spontaneous breathing efforts.

Table 1 displays the associated median elastance of all asynchronous breaths before and after reconstruction alongside the median of the non-asynchronous breaths. Range90 and mean absolute distribution (MAD) are also calculated for both the original and reconstructed set of breaths. n is the total number of asynchronous breaths in a given sample and h is the result of a two-sample Kolmogorov-Smirnov test with p-value < 0.05 implying a significant difference. The asynchronous area is the median of all breaths identified as asynchronous.

The cumulative distribution (CDF) plots for the original and reconstructed E of data samples, 3, 8, 9 and 10, are displayed in Figure 5. The asynchronous area for each sample is also plotted. Figure 4 shows E before and after reconstruction for all breaths in data sets 3, 8, 9 and 10, where reconstruction is expected to yield greater consistency as no MV parameters were changed during a 30 minute sample. Note that sample 9 contains only 31 non-asynchronous breaths, resulting in the jagged appearance of the non-asynchronous CDF line. Plots depicted in Figures 5 and 6 for all 10 data sets are attached in the online Appendix A for completeness.

Table 1. Flow Reconstruction Results

Data Sample	Number of AE Breaths (n)	Median Respiratory System Elastance, E_{rs} (cmH_2O/L)			MAD		Range90/ median		Async Area Median (%)
		Non AE*	AE (O)	AE (R)	(O)	(R)	(O)	(R)	
1+	181	27.42	17.51	23.76	5.71	4.03	0.80	0.57	18.16
2+	141	27.51	18.34	24.37	4.74	3.40	0.69	0.53	15.77
3+	246	24.46	15.58	23.23	5.64	3.32	0.88	0.61	19.48
4+	164	16.23	9.73	15.60	7.74	6.52	2.72	2.55	14.85
5+	194	28.88	23.17	25.96	9.75	7.29	1.65	1.12	17.06
6+	209	25.39	21.20	24.99	10.00	6.05	2.02	1.03	18.10
7+	273	22.35	9.49	16.62	12.63	6.15	2.36	1.22	16.19
8+	238	24.24	23.86	25.84	3.03	2.47	0.63	0.43	11.58
9+	469	36.86	27.28	33.91	8.61	5.21	0.67	0.52	24.53
10	1	16.16	15.82	16.85	1.03	1.03	0.18	0.18	6.52

* AE: Asynchronous breaths, O: Original airway flow, R: Reconstructed airway flow, + indicates $p<0.05$ comparing reconstructed respiratory elastance to baseline unreconstructed elastance using Kolmogorov-Smirnov test.

4.0 Discussion

In this study, all data samples with asynchronous events experienced a decrease in Range90/median E and MAD after flow reconstruction. The extent to which the E changes not only depends on the performance of the algorithm, but also on the number and magnitude of AEs. The median [maximum (max), minimum (min)] decrease in mean absolute deviation across these data samples, not including Data sample 10, which contained only one AE, was 29.4% (51%, 18.6%). A decrease in Range90/median or MAD indicates a decrease in variability of E due to asynchrony, and thus, improved the consistency of identification of patient specific, underlying respiratory mechanics. The median (max, min) decrease in the Range90 divided by median E was 30.7% (48.8%, 6.4%).

Dataset 10 contains a minimum amount of AEs and correspondingly has the smallest number of reconstructions. Thus, the Range90/median and MAD of E is minimal, indicating that the algorithm has a minimal effect on non-asynchronous breaths. This result can be seen in Figure 5, Sample 10, where all the three CDF lines are steep. This result is reiterated in the results of the Kolmogorov-Smirnov test, with all data sets having $p<0.05$ except for the non-asynchronous case of Data sample 10.

Performance of the algorithm in determining the true underlying respiratory system elastance can also be assessed by comparing the E of the reconstructed breaths to the E of non-reconstructed breaths. Breaths that have not been reconstructed are those which do not have upwards fluctuations in flow large enough to result in the model crossing the data at these points, or those which exhibit a high conformation to the model during the initial fit. These breaths are likely to not contain AEs. Therefore, the median of these breaths gives a measure of the underlying true E if no physiological or external processes, such as MV recruitment manoeuvers or change of ventilator settings, occur over the time period.

For the 9 data samples containing spontaneous breathing or AEs, 8 resulted in the median of the reconstructed E moving closer towards the true E. The median shift was 65.7% closer to the true E, from its original estimate, with a maximum of 89.5%. As a result, E for reconstructed breaths shifted from median 33.3% to 8% deviation from the true E.

After reconstruction, Data sample 8 did not see its E values improved after flow reconstruction, because the median E of the asynchronous breaths was already within 1.7% of the true E value. Thus, the flow reconstruction had a minimal change, as expected in such a case. Improvements in the consistency of elastance values, all else equal, gives evidence that the asynchrony magnitudes being calculated are accurate, resulting in reliable asynchrony detection and estimation.

The range of asynchronous magnitude for datasets used in this report range from 6.52% to 24.53%. The magnitude of asynchrony can vary between datasets containing similar amounts of asynchrony. This can be seen in Datasets 3 (246 AE) and 8 (238 AE), which had median asynchronous magnitudes of 19.48% and 11.58% respectively. The IIPR allows for asynchrony magnitudes to be accurately measured and quantified and for the possibility of further development in this area towards an aid to monitor patient recovery.

An interesting and unique consequence of the method is that the tidal volume may change after reconstructing the flow. This change can occur because during patient spontaneous breathing, the movement of the patient's diaphragm and intercostal muscles creates an elastance demand effect [30]. Therefore, during the asynchronous portion of a breath, where a patient is attempting to breathe in, there must be more volume to create the same pressure. Thus, for example, if this portion occurs at the end of inspiration, there is an increased tidal volume. However, the algorithm is attempting to reconstruct the flow or volume which would have resulted if the patient was not spontaneously breathing. This extra volume would thus 'disappear', as it would not have occurred in the absence of spontaneous breathing effort.

A limitation of the study is that the 'true' elastance had to be assumed to be the median elastance of non-asynchronous breaths. This 'true' elastance is likely to be accurate, as the underlying elastance of patients is not expected to vary significantly over a time period as short as 30 minutes, or per Figure 6, even shorter periods, because it is clear in the figure that the behaviour is stable. Thus, if variation did occur a clear trend in elastance would be expected in the elastance over time plots. An extension of this study in the future may be to utilize data pre and post sedation, so that a more reliable comparison to the true underlying patient elastance can be made, when the patient is sedated.

While the flow reconstruction has been shown to perform satisfactorily across multiple patients and asynchrony types, the performance of the algorithm has some limitations. Flow reconstruction is hindered by the multitude of possible asynchrony shapes, with the unaffected flow being difficult to determine even by eye. While the algorithm is capable of both lowering and raising apparent E towards a true underlying unaffected E value, it is more effective at raising a low E. This behavior may be due to the majority of ‘standard’ asynchronies resulting in a lowered apparent E. The more aberrant breaths, which the algorithm is unable to reconstruct effectively, often result in a raised E.

Of note is the presence of seemingly normal breaths that have E values significantly higher than the median, appearing in 2.5% of all breathing cycles. These breaths have inspiration flow curves which appear to be the standard ramp shape, however the peak flow may be lower than usual, or the time of inspiration may be abnormally short. Additionally, the inspiratory volume is often smaller than the expiratory volume. These breaths have a lower than normal tidal volume and therefore have a raised identified elastance. Because of the shape of the flow curve being undistorted, these breaths are not classed as asynchronous by the algorithm. Breaths such as these result in the 7 ‘outlier’ values seen in Dataset 10, and the period between breaths 200-400 in Dataset 7 where there are breaths with high elastance values. Interestingly, in Dataset 7 the seemingly non-asynchronous breaths with abnormally low tidal volumes are generally followed or preceded by highly asynchronous breaths with negative initial elastance estimates. These ‘catch-up’ breaths may have high identified elastance values due to activity of the diaphragm that is not visible in the shape of the curve and demonstrates a limitation of the algorithm, which relies on geometric abnormalities in the flow curve.

This method currently only applies to square wave pressure delivery. However, this is a commonly used pressure shape which is present on many different ventilators. As such, the method applies to a range of ventilators. The method may also be adapted to other pressure shapes.

While flow reconstruction is currently not as effective for some types of asynchronies, determination of a true unaffected, underlying E is improved in all cases seen in this study. Because the algorithm works on single breaths, it is able to be utilized in situations where every breath is asynchronous, or where there is only a short time period available to identify respiratory mechanics, such as during PEEP recruitment manoeuvers [26]. Therefore, the algorithm exhibits the potential for improvement for guiding MV using model-identified respiratory mechanics. Further improvements may be possible by considering further types of asynchrony and changing the way early asynchronies are handled.

5.0 Conclusion

The proposed iterative interpolative flow reconstruction algorithm is able to improve respiratory system elastance estimation for a wide variety of flow anomaly cases during pressure controlled ventilation. These results have shown the potential use of respiratory mechanics to guide MV therapy in this ventilation mode. Equally importantly, reconstruction allows for an effective measure of asynchrony magnitude, which will enable improved monitoring of patient-ventilator interaction and assessment of the impact of AEs on outcomes given an automated detection and quantification method. Additionally, IIFR allows an objective quantification of asynchrony event magnitude which can be used in future studies or in intensive care. The algorithm allows for a more optimized and efficient MV therapy and thereby has a potential to improve patient outcomes in intensive care.

6.0 Main Outcomes

1) A novel iterative flow reconstruction method is presented and validated (on clinical data)

2) Method enables improved estimation of underlying elastance to guide MV

3) Automated detection and (first ever) quantification of AEs will enable further study of impact on clinical outcomes.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgement

The authors would like to thank the Health Research Council of New Zealand (Grant Number: 13/213) and the Canterbury Intensive Care Research and Education Trust for funding this research.

References

1. Ranieri VM, Giunta F, Suter PM, Slutsky AS: **Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome**. *JAMA* 2000, **284**:43 - 44.
2. Hasan A: **Understanding Mechanical Ventilation: A Practical Handbook**, 2nd edn: Springer; 2010.
3. Girard TD, Bernard GR: **Mechanical Ventilation in ARDS**. *Chest* 2007, **131**(3):921-929.
4. Slutsky AS: **Lung Injury Caused by Mechanical Ventilation***. *Chest* 1999, **116**(suppl 1):9S-15S.
5. Lucangelo U, Pelosi P, Zin W, Aliverti A, Crimi E, Sorbo L, Ranieri VM: **Ventilator-Associated Lung Injury**. In: *Respiratory System and Artificial Ventilation.* edn.: Springer Milan; 2008: 119-137.
6. Esteban A, Frutos F, Tobin MJ, Alía I, Solsona JF, Valverdu V, Fernández R, de la Cal MA, Benito S, Tomás R *et al*: **A Comparison of Four Methods of Weaning Patients from Mechanical Ventilation**. *New England Journal of Medicine* 1995, **332**(6):345-350.
7. Akoumianaki E, Lyazidi A, Rey N, Matamis D, Perez-Martinez N, Giraud R, Mancebo J, Brochard L, Richard J-CM: **Mechanical ventilation-induced reverse-triggered breaths: A frequently unrecognized form of neuromechanical coupling**. *CHEST* 2013, **143**(4):927-938.
8. Blanch L, Villagra A, Sales B, Montanya J, Lucangelo U, Luján M, García-Esquirol O, Chacón E, Estruga A, Oliva J *et al*: **Asynchronies during mechanical ventilation are associated with mortality**. *Intensive Care Medicine* 2015, **41**(4):633-641.
9. de Wit M, Miller KB, Green DA, Ostman HE, Gennings C, Epstein SK: **Ineffective triggering predicts increased duration of mechanical ventilation ***. *Critical Care Medicine* 2009, **37**(10):2740-2745.
10. Epstein SK: **How Often Does Patient-Ventilator Asynchrony Occur and What Are the Consequences?** *Respiratory Care* 2011, **56**(1):25-38.
11. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH: **Mechanical Ventilation Guided by Esophageal Pressure in Acute Lung Injury**. *New England Journal of Medicine* 2008, **359**(20):2095-2104.
12. Brochard L, Martin G, Blanch L, Pelosi P, Belda FJ, Jubran A, Gattinoni L, Mancebo J, Ranieri VM, Richard J-C *et al*: **Clinical review: Respiratory monitoring in the ICU - a consensus of 16**. *Critical Care* 2012, **16**(2):219.
13. v Neergaard K, Wirz K: **Die Messung der Stromungswiderstande in den Atemwegen des Menschen insbesondere bei Asthma und Emphysem**. *Z Klin Med Berl* 1927:51 - 82.
14. Gottfried S, Higgs B, Rossi A, Carli F, Mengeot P, Calverly P, Zocchi L, Milic-Emili J: **Interrupter technique for measurement of respiratory mechanics in anesthetized humans**. *Journal of Applied Physiology* 1985, **59**(2):647-652.
15. Bates J, Milic-Emili J: **The flow interruption technique for measuring respiratory resistance**. *J Crit Care* 1991, **6**(4):227-238.
16. Younes M, Kun J, Masiowski B, Webster K, Roberts D: **A Method for Noninvasive Determination of Inspiratory Resistance during Proportional Assist Ventilation**. *Am J Respir Crit Care Med* 2001, **163**(4):829-839.
17. Criée CP, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, Berdel D, Köhler D, Magnussen H, Marek W *et al*: **Body plethysmography – Its principles and clinical use**. *Respiratory Medicine* 2011, **105**(7):959-971.

18. Fisher AB, DuBois AB, Hyde RW: **Evaluation of the forced oscillation technique for the determination of resistance to breathing**. *Journal of Clinical Investigation* 1968, **47**(9):2045.
19. Oostveen E, MacLeod D, Lorino H, Farré R, Hantos Z, Desager K, Marchal F, Measurements obotETFoRI: **The forced oscillation technique in clinical practice: methodology, recommendations and future developments**. *European Respiratory Journal* 2003, **22**(6):1026-1041.
20. Kostic P, Zannin E, Andersson Olerud M, Pompilio P, Hedenstierna G, Pedotti A, Larsson A, Frykholm P, Dellaca R: **Positive end-expiratory pressure optimization with forced oscillation technique reduces ventilator induced lung injury: a controlled experimental study in pigs with saline lavage lung injury**. *Critical Care* 2011, **15**(3):R126.
21. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, Pelosi P, Talmor D, Grasso S, Chiumello D *et al*: **The Application of Esophageal Pressure Measurement in Patients with Respiratory Failure**. *American Journal of Respiratory and Critical Care Medicine* 2014, **189**(5):520-531.
22. Brochard L: **Measurement of esophageal pressure at bedside: pros and cons**. *Current Opinion in Critical Care* 2014, **20**(1):39-46.
23. Redmond DP, Major V, Corbett S, Glassenbury D, Beatson A, Szlavecz A, Chiew YS, Shaw GM, Chase JG: **Pressure reconstruction by eliminating the demand effect of spontaneous respiration (PREDATOR) method for assessing respiratory mechanics of reverse-triggered breathing cycles**. In: *Biomedical Engineering and Sciences (IECBES), 2014 IEEE Conference on: 8-10 Dec. 2014 2014*; 2014: 332-337.
24. Rigo V, Graas E, Rigo J: **Automated respiratory cycles selection is highly specific and improves respiratory mechanics analysis**. *Pediatric Critical Care Medicine* 2012, **13**(4):e234-e239 210.1097/PCC.1090b1013e318238b318162.
25. Vicario F, Albanese A, Karamolegkos N, Wang D, Seiver A, Chbat N: **Noninvasive Estimation of Respiratory Mechanics in Spontaneously Breathing Ventilated Patients: A Constrained Optimization Approach**. *IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING* 2015.
26. Szlavecz A, Chiew Y, Redmond D, Beatson A, Glassenbury D, Corbett S, Major V, Pretty C, Shaw G, Benyo B *et al*: **The Clinical Utilisation of Respiratory Elastance Software (CURE Soft): a bedside software for real-time respiratory mechanics monitoring and mechanical ventilation management**. *BioMedical Engineering OnLine* 2014, **13**(1):140.
27. Stevenson D, Revie J, Chase JG, Hann CE, Shaw GM, Lambermont B, Ghuysen A, Kolh P, Desaive T: **Algorithmic processing of pressure waveforms to facilitate estimation of cardiac elastance**. *Biomedical engineering online* 2012, **11**(1):28.
28. Chiew YS, Chase JG, Shaw G, Sundaresan A, Desaive T: **Model-based PEEP Optimisation in Mechanical Ventilation**. *BioMedical Engineering OnLine* 2011, **10**(1):111.
29. Moorhead K, Piquilloud L, Lambermont B, Roeseler J, Chiew Y, Chase JG, Revelly J-P, Bialais E, Tassaux D, Laterre P-F *et al*: **NAVA enhances tidal volume and diaphragmatic electro-myographic activity matching: a Range90 analysis of supply and demand**. *Journal of Clinical Monitoring and Computing* 2013, **27**(1):61-70.

30. Chiew YS, Pretty C, Docherty PD, Lambermont B, Shaw GM, Desaive T, Chase JG: **Time-Varying Respiratory System Elastance: A Physiological Model for Patients Who Are Spontaneously Breathing**. *PLoS ONE* 2015, **10**(1):e0114847.

Figure Legend

Figure 1 (Single Column). Example airway flow and pressure plot for a normal and asynchronous breath

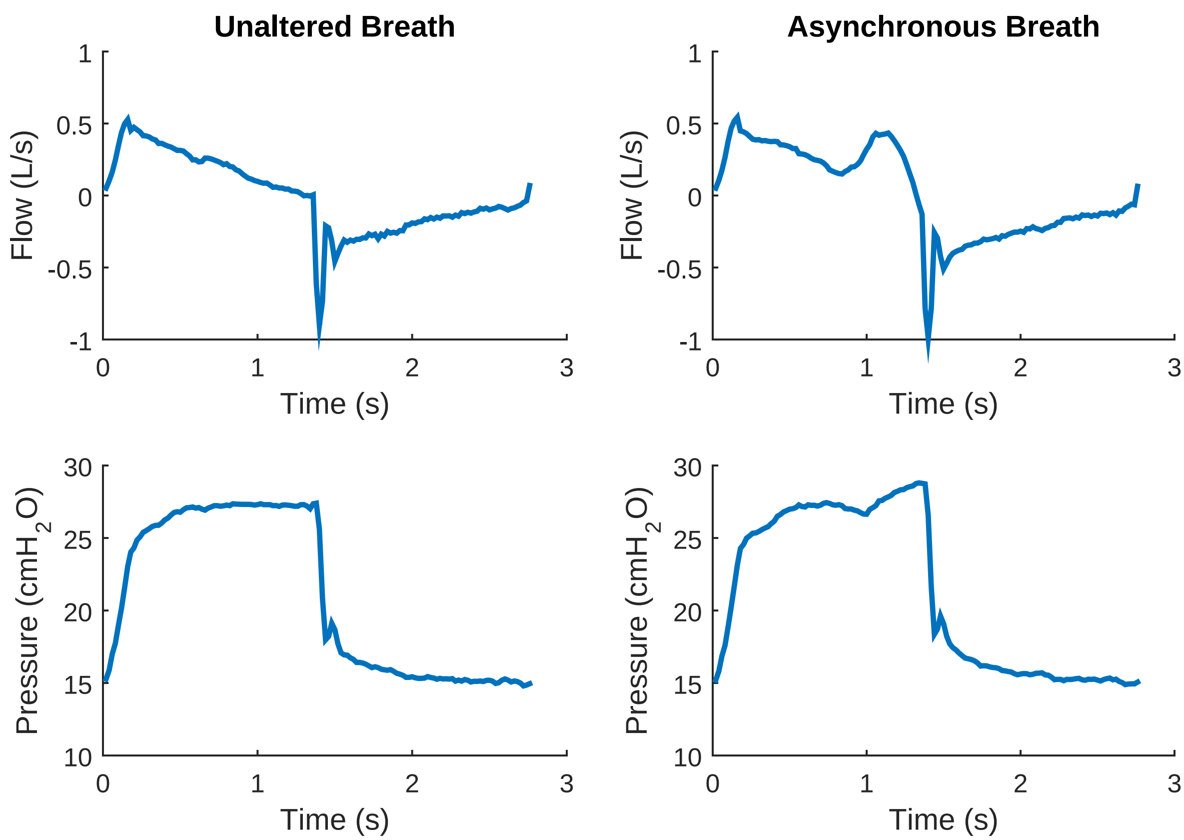
Figure 2 (Two Column). Airway flow or pressure plots for each step of iterative interpolative flow reconstruction process

Figure 3 (Two Column). Flow reconstruction process

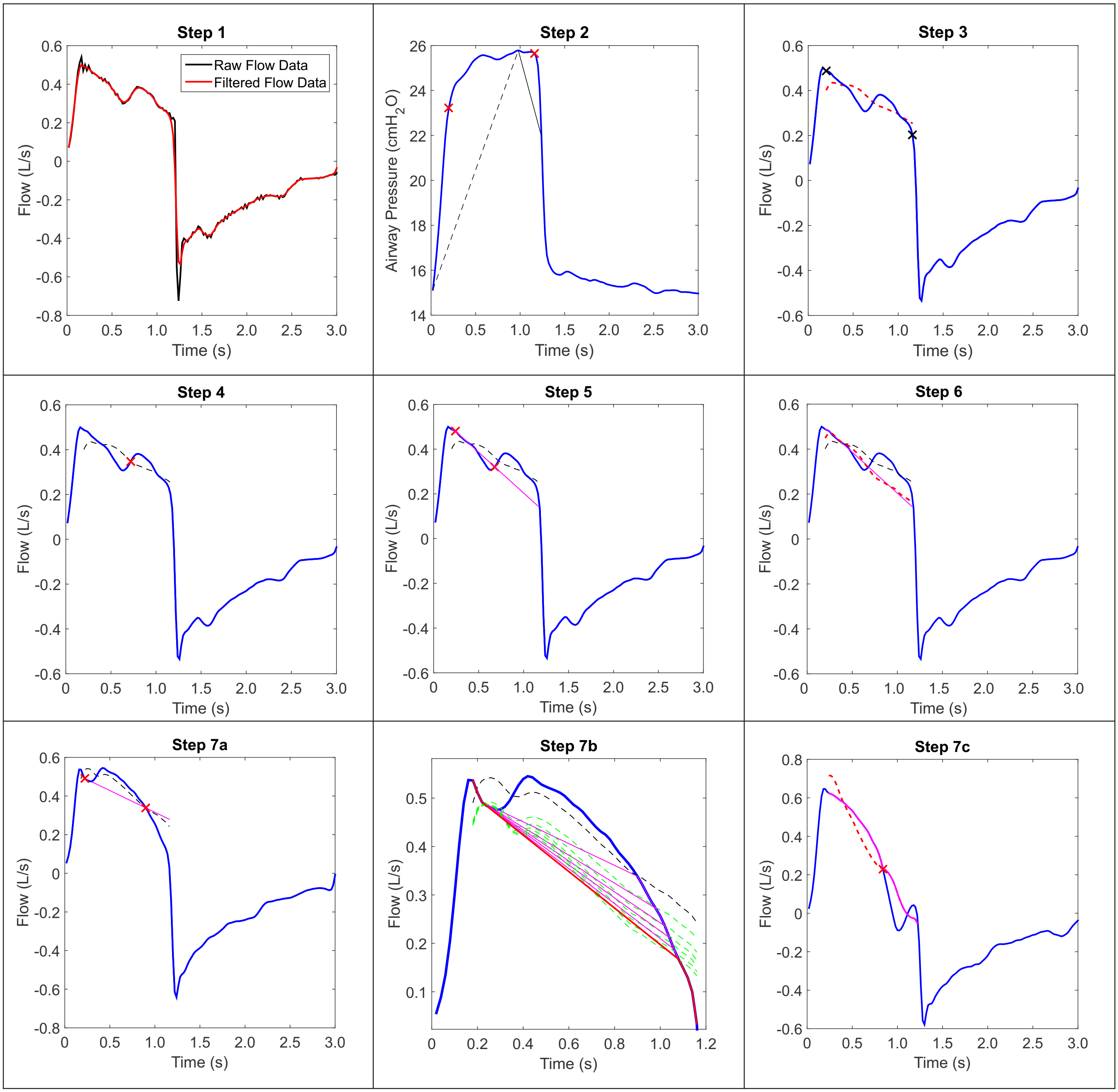
Figure 4 (Single Column). Example reconstructions for different asynchrony shapes, encountered in three different patients

Figure 5 (Two Column). CDF plots of elastance for the initial and reconstructed breaths affected by AEs, breaths without AEs and asynchronous area for data sets 3, 7, 9 and 10.

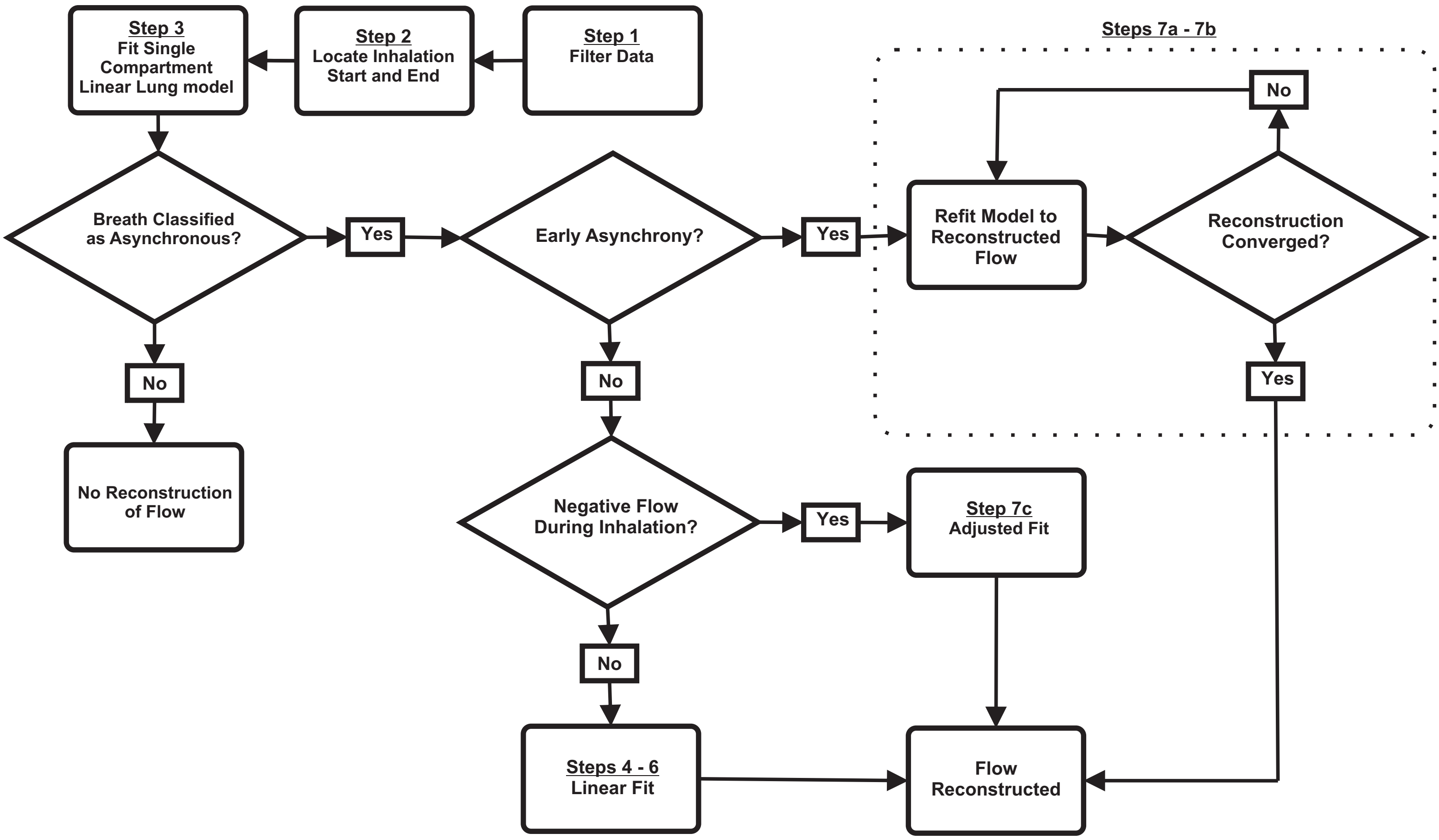
Figure 6 (Two Column). Plots of elastance for the initial and reconstructed breaths for data sets 3, 7, 9 and 10, where ‘x’ is the elastance using the given data, and ‘o’ using reconstructed data.

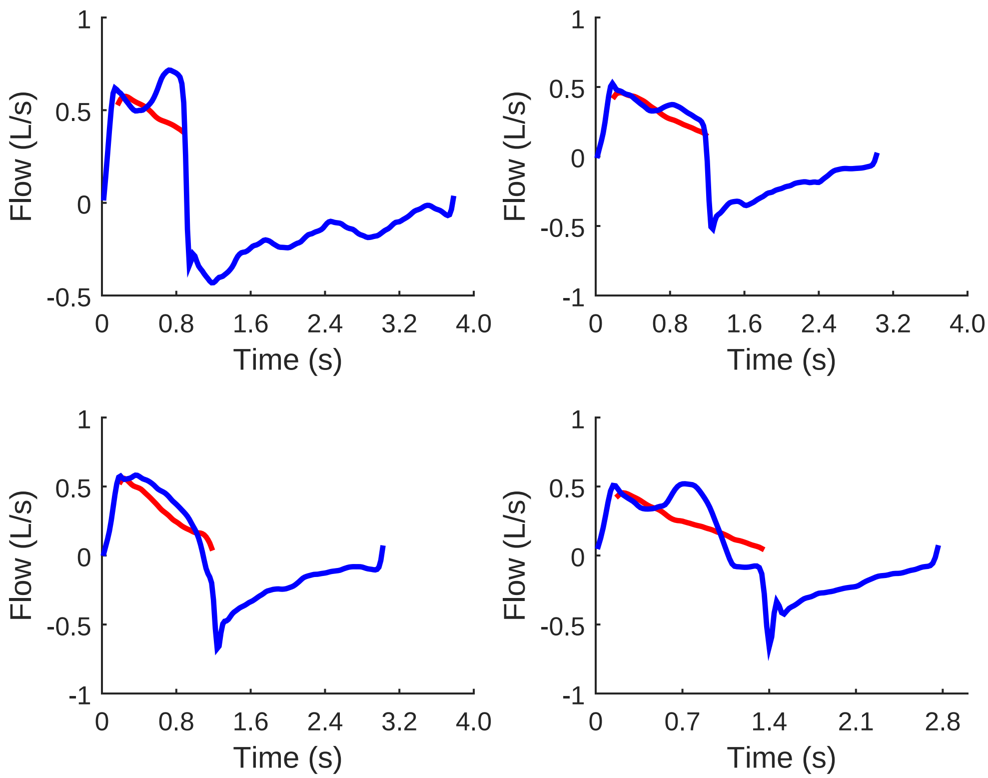


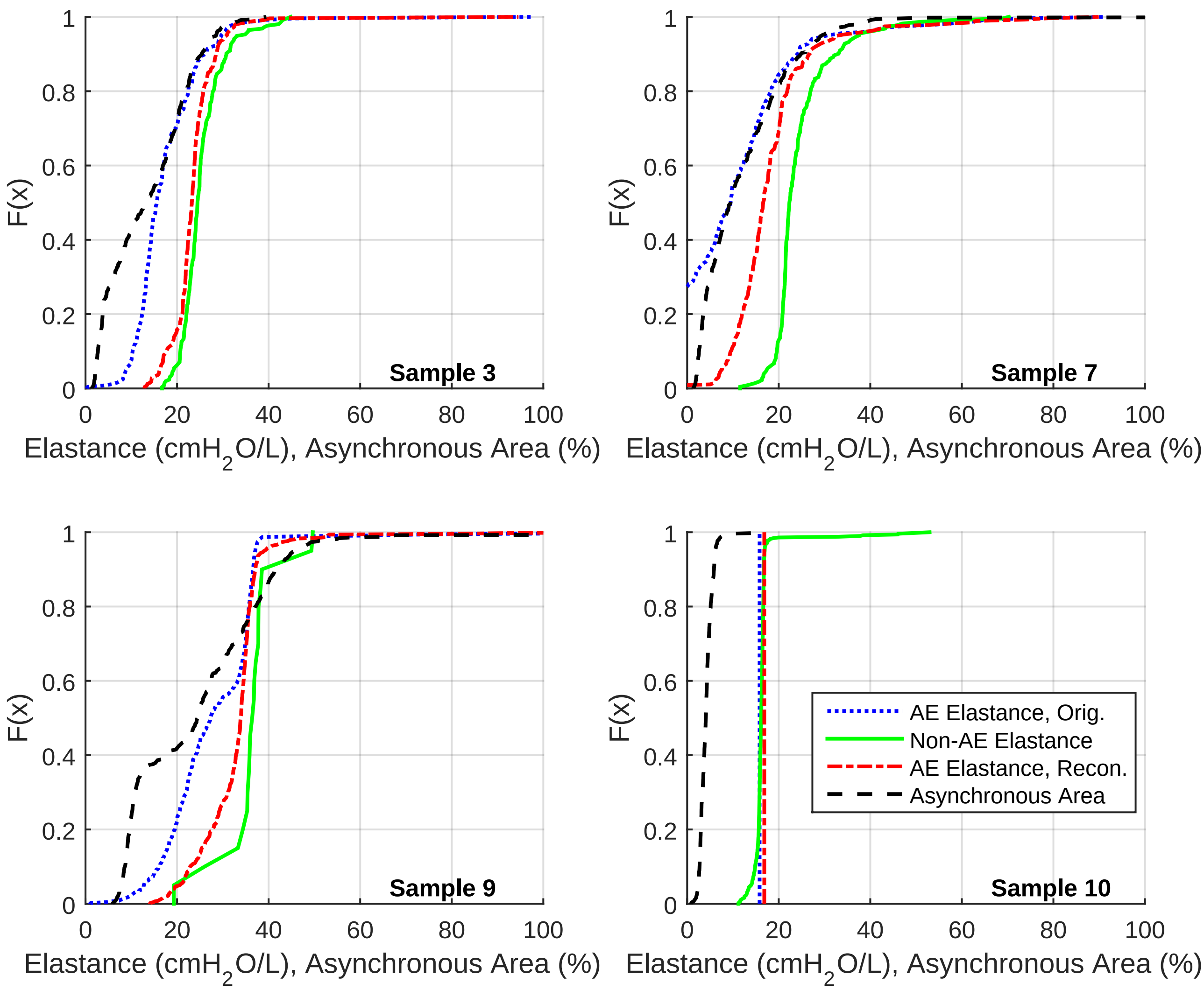
Unaltered Breath
Asynchronous Breath
Flow (L/s)
1
0.5
0
-0.5
-1
Time (s)
0
1
2
3
Pressure (cmH$_2$O)
30
25
20
15
10

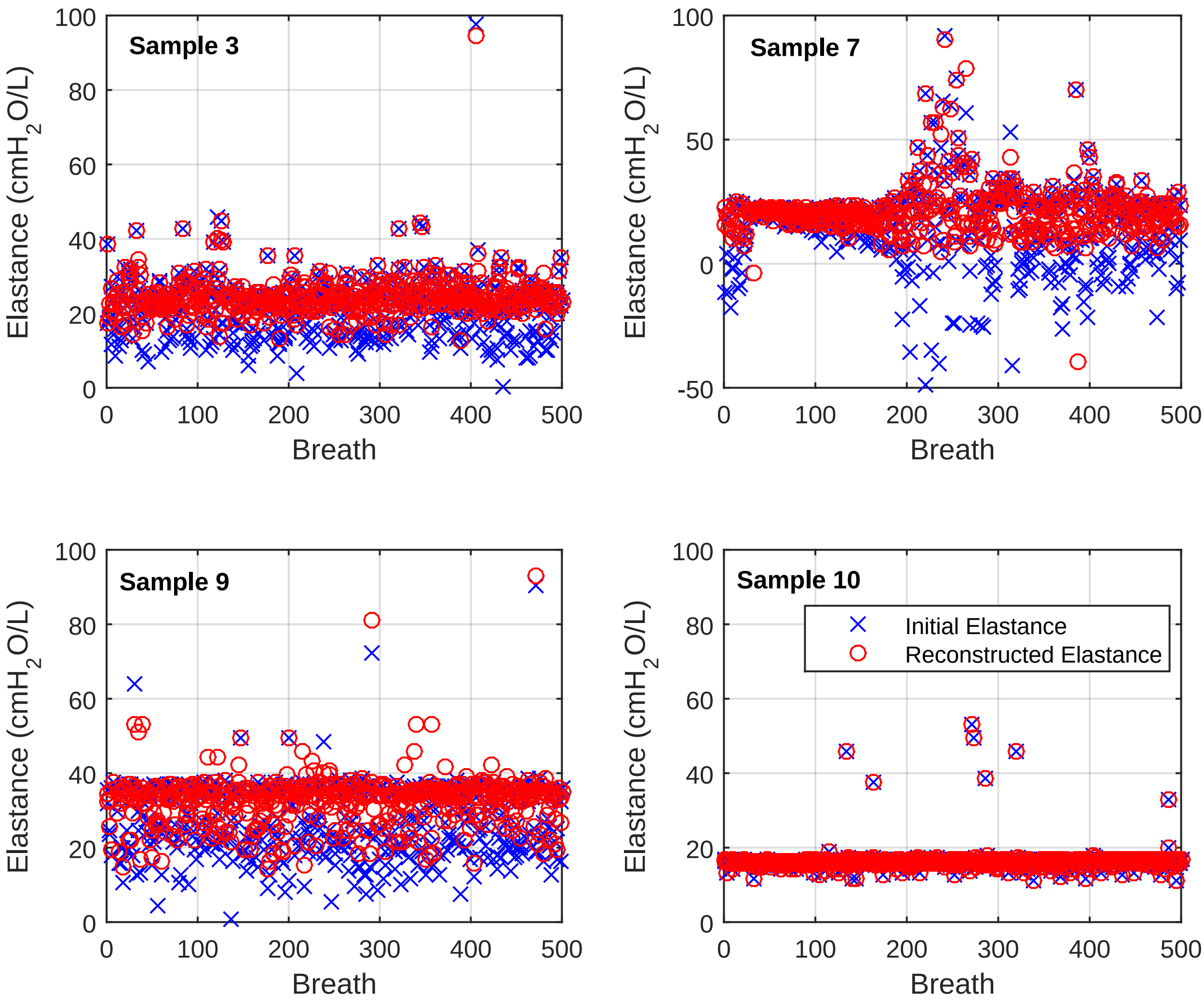


Step 1
Raw Flow Data
Filtered Flow Data
Flow (L/s)
Time (s)
Step 2
Airway Pressure (cmH2O)
Time (s)
Step 3
Flow (L/s)
Time (s)
Step 4
Flow (L/s)
Time (s)
Step 5
Flow (L/s)
Time (s)
Step 6
Flow (L/s)
Time (s)
Step 7a
Flow (L/s)
Time (s)
Step 7b
Flow (L/s)
Time (s)
Step 7c
Flow (L/s)
Time (s)


Step 3
Fit Single Compartment Linear Lung model
Step 2
Locate Inhalation Start and End
Step 1
Filter Data
Steps 7a - 7b
No
Breath Classified as Asynchronous?
Yes
Early Asynchrony?
Yes
Refit Model to Reconstructed Flow
Reconstruction Converged?
No
No
Yes
No Reconstruction of Flow
Negative Flow During Inhalation?
Yes
Step 7c
Adjusted Fit
No
Steps 4 - 6
Linear Fit
Flow Reconstructed


1
0.5
0
-0.5
Flow (L/s)
0
0.8
1.6
2.4
3.2
4.0
Time (s)
1
0.5
0
-0.5
-1
Flow (L/s)
0
0.8
1.6
2.4
3.2
4.0
Time (s)
1
0.5
0
-0.5
-1
Flow (L/s)
0
0.8
1.6
2.4
3.2
4.0
Time (s)
1
0.5
0
-0.5
-1
Flow (L/s)
0
0.7
1.4
2.1
2.8
Time (s)


Sample 3
Sample 7
Sample 9
Sample 10
F(x)
Elastance (cmH2O/L), Asynchronous Area (%)
AE Elastance, Orig.
Non-AE Elastance
AE Elastance, Recon.
Asynchronous Area


Sample 3
Sample 7
Sample 9
Sample 10
Initial Elastance
Reconstructed Elastance
Elastance (cmH2O/L)
Breath